

### **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application;

### **Listing of Claims:**

Claims 1-149 are currently cancelled.

New claims 150-187 have been added.

150. (New) A method of identifying an agent that ameliorates or modulates a phenotype or neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality, associated with a disruption in the gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype or disorder resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to said non-human transgenic animal; and

(e) determining whether said test agent ameliorates or modulates the phenotype or neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in the non-human transgenic animal.

151. (New) The method of Claim 150, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

152. (New) The method of Claim 150, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

153. (New) The method of Claim 150, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

154. (New) The method of Claim 150, wherein the eye abnormality is a retinal abnormality.

155. (New) The method of Claim 150, wherein the eye abnormality is consistent with vision problems or blindness.

156. (New) The method of Claim 150, wherein the eye abnormality is consistent with retinal degeneration or retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia

spondyloepiphysaria congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

157. (New) The method of Claim 150, wherein the eye abnormality is a cataract.

158. (New) The method of Claim 157, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

159. (New) The method of Claim 150, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

160. (New) The method of Claim 150, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

161. (New) The method of Claim 150, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation-associated diseases including graft rejection and graft -versus-host disease.

162. (New) The method of Claim 150, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

163. (New) The method of Claim 150, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing; an increased mean artery-to-vein ratio associated with retinal degeneration; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level;

a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrae; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgG1, IgG2a, IgG2b and IgG3 levels.

164. (New) An agent identified by the method of Claim 150.

165. (New) The agent of Claim 164 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

166. (New) The agent of Claim 165, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

167. (New) The agent of Claim 165, wherein the antagonist is an anti-anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

168. (New) A method of ameliorating or modulating a phenotype or neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already have the phenotype or disorder, or may be prone to have the phenotype or disorder, or may be in whom the phenotype or disorder is to be prevented, an effective amount of the agent of Claim 164, or agonists or antagonists thereof, thereby effectively ameliorating or modulating the phenotype or disorder.

169. (New) A method of evaluating a therapeutic agent capable of affecting a condition or neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality, associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) evaluating the effects of the test agent on the identified condition or disorder associated with gene disruption in the non-human transgenic animal.

170. (New) A therapeutic agent identified by the method of Claim 169.

171. (New) The therapeutic agent of Claim 170 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

172. (New) The therapeutic agent of Claim 171, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

173. (New) The therapeutic agent of Claim 171, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

174. (New) A pharmaceutical composition comprising the therapeutic agent of Claim 170.

175. (New) A method of treating or preventing or ameliorating a condition or neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO224, PRO9783, PRO1108,

PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the condition or disorder, or may be prone to have the condition or disorder or may be in whom the condition or disorder is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 170, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said condition or disorder.

176. (New) The method of Claim 169, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

177. (New) The method of Claim 169, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

178. (New) The method of Claim 169, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

179. (New) The method of Claim 169, wherein the eye abnormality is a retinal abnormality.

180. (New) The method of Claim 169, wherein the eye abnormality is consistent with vision problems or blindness.

181. (New) The method of Claim 169, wherein the eye abnormality is consistent with retinal degeneration or retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM),



meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

182. (New) The method of Claim 169, wherein the eye abnormality is a cataract.

183. (New) The method of Claim 182, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

184. (New) The method of Claim 169, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

185. (New) The method of Claim 169, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e.g., hemangioma (capillary and

cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

186. (New) The method of Claim 169, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft -versus-host disease.

187. (New) The method of Claim 169, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.